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REVIEW

BRI2 as an anti-Alzheimer gene

Shuji Matsuda[1] · **Takao Senda**[1]

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Abstract
There are several theories regarding the etiologies of Alzheimer disease (AD). Considering that all genes responsible for familial AD are amyloid protein precursor (APP) or APP metabolizing enzymes, surely aberrant APP metabolism is crucial to pathogenesis of AD. BRI2, a type II transmembrane protein, binds APP and inhibits all α, β, and γ pathways of APP proteolysis. Crossing AD model mice with BRI2 transgenic or BRI2 knockout mice confirmed that BRI2 is an anti-Alzheimer gene. Mutations of BRI2 are known to cause rare familial dementias in human. Analysis of knock-in mice harboring the disease mutation revealed the memory defect in the mice, attributable to loss of protective function of BRI2. Further studies are needed to decipher this anti-Alzheimer mechanism of BRI2 to develop a novel therapeutic application for AD. In this review, after describing basic assumptions in AD study, we focus on BRI2 as an anti-Alzheimer gene.

Keywords Alzheimer disease · Amyloid protein precursor · BRI2 · Processing · Familial British dementia · Familial Danish dementia

Background

Alzheimer disease, sporadic AD, and Down syndrome

Alzheimer disease (AD) was discovered a century ago [1]. In his 1907 paper, Alois Alzheimer described a 51-year-old woman with progressive dementia. The postmortem examination of the brain showed amyloid plaques and neurofibrillary tangles (NFTs) with atrophied brain due to neuronal loss. Amyloid plaques, sometimes called senile plaques in older patients, are large extracellular deposits of protein aggregates. Intracellular NFTs were later identified as hyperphosphorylated tau, a microtubule-associated protein. These three symptoms, amyloid plaques, NFTs, and neuronal loss are the major hallmarks of AD.

Some forms of senile dementia with an onset age > 65 also share those three traits of AD. These are called sporadic AD in contrast to early onset familial AD (FAD) initially described by Alzheimer. FAD comprises about 2% of total AD cases [2].

✉ Shuji Matsuda
smatsuda@gifu-u.ac.jp

[1] Department of Anatomy, Graduate School of Medicine, Gifu University, 1-1 Yanagido, Gifu, Gifu 501-1194, Japan

Down syndrome, trisomy of chromosome 21, has been shown to display the same three features of AD. At the same time, the chromosome happens to harbor amyloid precursor protein (APP), which is one of the causative genes of AD [3]. Furthermore, a short duplication of APP region is enough to cause the early onset AD [4]. Therefore, it is generally believed that FAD, sporadic AD, and Down syndrome share the essence of AD, even though their clinical manifestations vary.

Discovery of APP

Pathogenesis of AD had been enigmatic for a long time since its discovery. The breakthrough came with the purification of β amyloid (Aβ), the major component of amyloid deposits. The short, approximately 40 amino acid peptide was used to clone the gene of its precursor, APP. The cloned gene encoded a type I single transmembrane protein, which is a receptor like molecule of ~700 amino acids, surprisingly large for a short peptide [5].

In mammals, APP has two other homologs: APLP1 and APLP2 [6, 7]. All members of the APP family share the distinct GYENPTY cytoplasmic motif and are single-pass type-I membrane proteins. APLPs lack Aβ sequence and do not produce Aβ.

To produce Aβ, APP is initially cleaved by β secretase extracellularly, which releases a soluble fragment (sAPPβ). The remaining membrane bound fragment consisted of C-terminal 99 amino acids (C99) is further cleaved by γ secretase to produce APP intracellular domain (AICD) and Aβ peptides of varying lengths, including the major 40 amino acid peptide (Aβ40), and minor 42 amino acid peptide (Aβ42). APP undergoes different, non-amyloidogenic processing by α secretase, in which case APP is initially cleaved within the Aβ sequence, precluding the production of Aβ. The remaining 83 amino acid fragment (C83) is again cleaved by γ secretase to produce AICD and p3, which does not form aggregation (Fig. 1). The majority of APP is metabolized via α pathway, not β pathway. The unusual reaction of γ secretase is called intramembranous proteolysis: the enzyme cleaves the protein within the transmembrane region, where water molecules used for peptide bond hydrolysis are scarce by definition.

The etiologies of AD

There are four distinct theories regarding the pathogenesis of AD. With all its defects and modifications, amyloid cascade theory is most popular to this day.

(1) Amyloid cascade. Aβ, which is accumulated in AD brains, elicits toxic downstream reactions including oxidative stress, leading to AD [8, 9]. *APP, PSEN1*, and *PSEN2*, the causative genes of FAD, are all involved in APP processing and production of Aβ [10]. In fact, synthetic Aβ is toxic to synaptic functions of hippocampal neurons, which could represent an early signs of AD [11]. In short, this theory proposes that AD produces toxic Aβ, which, in turn, causes other symptoms of AD.

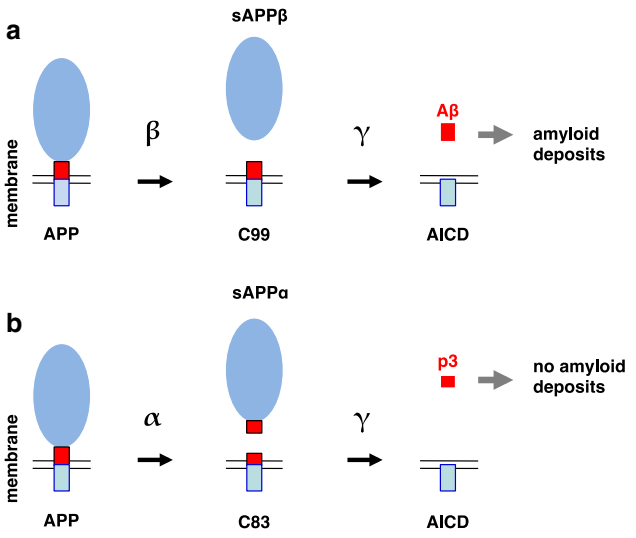

Fig. 1 Schematic representation of APP processing. **a** To produce Aβ, APP is first cleaved by β secretase and releases soluble APP β (sAPPβ, blue). The remaining C-terminal 99 amino acids (C99) are further processed by γ secretase to produce APP intracellular domain (AICD) and Aβ, which form amyloid deposits. **b** Alternatively, APP is cleaved within the Aβ sequence (red) by α secretase to release soluble APP α (sAPPα, blue + red). The remaining C-terminal 83 amino acid fragment (C83) is similarly cleaved by γ secretase to produce AICD and p3, which does not form aggregates

Unfortunately, amyloid lesion does not correlate well with AD stages [12]; and APP and PSEN mutants found in FAD pedigrees are not always over-producing Aβ. The latter apparent contradiction was rationalized by the increased ratio of Aβ42: Aβ40 found in most AD mutants [10]. How the ratio, not the absolute amount, becomes important may be probably circumvented by propagation of toxic Aβ as in prion disease [13, 14]. Recently, this theory diverged to the proposition that oligomeric forms of Aβ are the true culprit, but not monomers or multimers [9]. So far, clinical attempts to lower Aβ burden in patients failed [15].

(2) APP is a receptor. On ligand binding, Notch is intramembranously cleaved, releasing its notch intracellular domain (NICD) for translocation to nucleus for downstream signals. SREBP2, a regulator of cholesterol metabolism, is also intramembranously cleaved, and resulting intracellular domain is translocated to the nucleus activating downstream signals. By analogy, AICD could be a signal transducer [16].

Indeed, in artificial systems, AICD has a potential to activate downstream targets after its translocation to nuclei [17]. Several APP ligands have been proposed, including DR6, F-spondin, netrin-1, reelin, and pancortin-1, but none of them showed robust ligand-dependent proteolysis of APP [18], or no mutations linked AD were found in them [19]. There are only three known early onset FAD genes, namely *APP, PSEN1*, and *PSEN2*; one clear late onset risk gene, *APOE*. A dozen of risk genes discovered by genome-wide association study of sporadic AD increased the risk of AD about 20% at best [10]. No natural downstream targets have been established so far [20].

(3) It is not APP, it is tau. Tau phosphorylation correlates well with disease stages of AD [12]. Moreover, genetic tau mutations (FTDP-17) show AD-like phenotype except that they do not have Aβ deposits [21]. It is difficult to resolve the relationship with tau and Aβ, because all rodent models of AD do not show NFTs without a concomitant expression of mutant tau.

(4) Abnormal axonal transport is the cause. APP is axonally transported by kinesin motor. Kinesin light chain is reported to bind APP directly, which makes APP a receptor for axonal transport cargo [22, 23]. However, controversy still remains on this one [24–26].

Identification of BRI2 as anti-Alzheimer gene

BRI2 binds APP and inhibits all three pathways of APP metabolism

"APP as a receptor" theory in mind, split-ubiquitin yeast two hybrid screening was used to identify APP-interacting molecules including transmembrane proteins. After cloned into a mammalian expression vector, candidates were tested for their interaction in transfected cells. Out of many, only BRI3 and CD74 were positive, both of which were single transmembrane type II proteins [27, 28]. BRI3 has a close homolog, BRI2, which is a causative gene of rare AD-like dementia [29]. The interaction of BRI2 and APP was tested and turned out to be positive [30]. Others obtained similar results, as well [31].

In addition to binding, overexpression of BRI2 increased C99, the β pathway product, which indicates that BRI2 changes processing of APP. BRI2 binds C99 but not C83. Accordingly, BRI2 inhibits γ cleavage of C99, but not that of C83. This change in APP processing was not observed with BRI3 or CD74. Even though BRI2 shares a large BRICHOS domain with BRI3, the minimal region required for the interaction was a short juxtamembrane region that does not contain the BRICHOS domain [32]. BRI2 does not bind APLPs, but exchanging 33 amino acid segment of APLPs with the APP counterpart makes both behave like APP [33]. Combination of various cellular assays showed that BRI2 inhibits all of α, β and γ pathways, when BRI2 can bind to the substrate (Fig. 2a). In mouse neuroblastoma N2A cells, the majority of BRI2 appears to be on the cell surface, and APP is inside, suggesting that APP and BRI2 encounter at certain routes, probably from the cell surface to endocytic pathway [34] (Fig. 2b).

Crossing transgenic BRI2 mice with AD model mice decreased Aβ deposits. When BRI2 knockout mice (BRI2 −/+ and BRI2 −/−) were crossed with AD model mice, APP metabolites including Aβ increased [33]. All these indicate that endogenous BRI2 functions as an anti-Alzheimer gene in animals.

Contrary to a report that BRI2 binds β secretase [35], BRI2 did not bind to any component of β or γ secretases tested in our hands [33].

Mutations of BRI2 cause hereditary dementias

BRI2 was initially cloned as ITM2B, a type II single-pass transmembrane protein with unknown functions [36]. BRI2 and its two other homologs, BRI1 (ITM2A) and BRI3 (ITM2C), share their basic topology and constitute

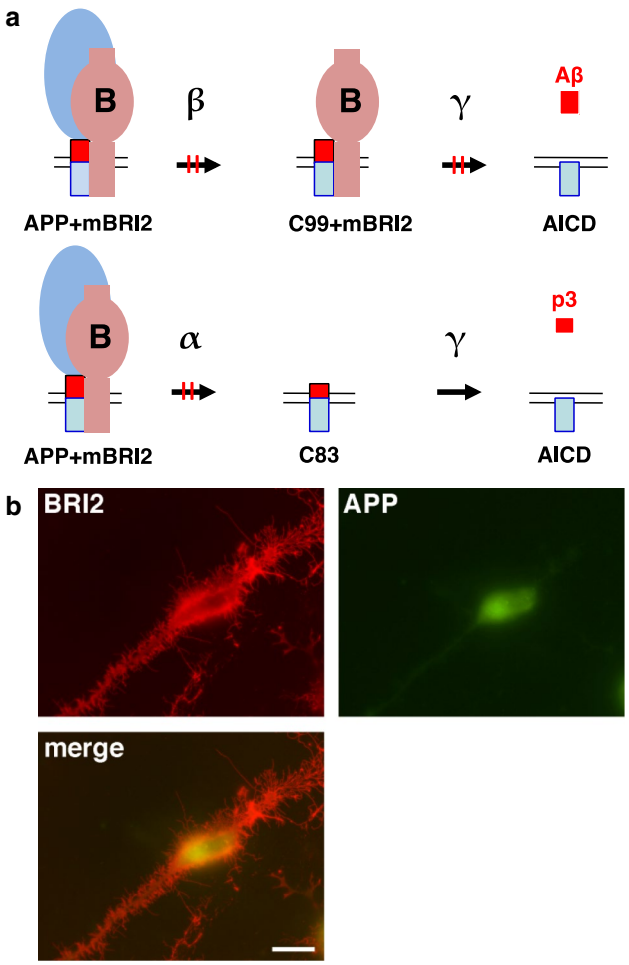

Fig. 2 Inhibition of APP processing by BRI2 and localization of BRI2 and APP. **a** Mature BRI2 binds APP and C99, and inhibits further processing of these two. BRI2 does not bind C83 and it does not inhibit its cleavage by γ secretase. **b** Localization of transfected BRI2 and APP in differentiated N2A cells. Confocal microscopy shows the majority of BRI2 appears to be on micro-processes near the bottom of the cell, whereas the majority of APP resides within the cell body. Bar = 10 μm

a family of proteins with the shared BRICHOS domain. BRI3 is dominantly expressed in neurons, BRI2 is ubiquitous, and BRI1 expression is confined to chondrocytes. The function of this BRICHOS domain remains unclear, though it might work as a protein chaperone [37].

BRI2 becomes mature by proteolysis, which secretes its C-terminal short peptide (BRI2-23) (Fig. 3a) [38, 39]. The extracellular domain of mature BRI2 is shed by ADAM-10-like proteases and then processed by SSPL2a/b [40]. SSPL2 is an intramembranous protease similar to γ secretase, with opposite inside-outside topology to that of γ secretase [41].

The first link of BRI2 to dementia came with the discovery that the amyloid deposits of rare familial dementia (familial British dementia—FBD) are caused by mutation of BRI2 [29]. FBD is a rare heritable dementia with

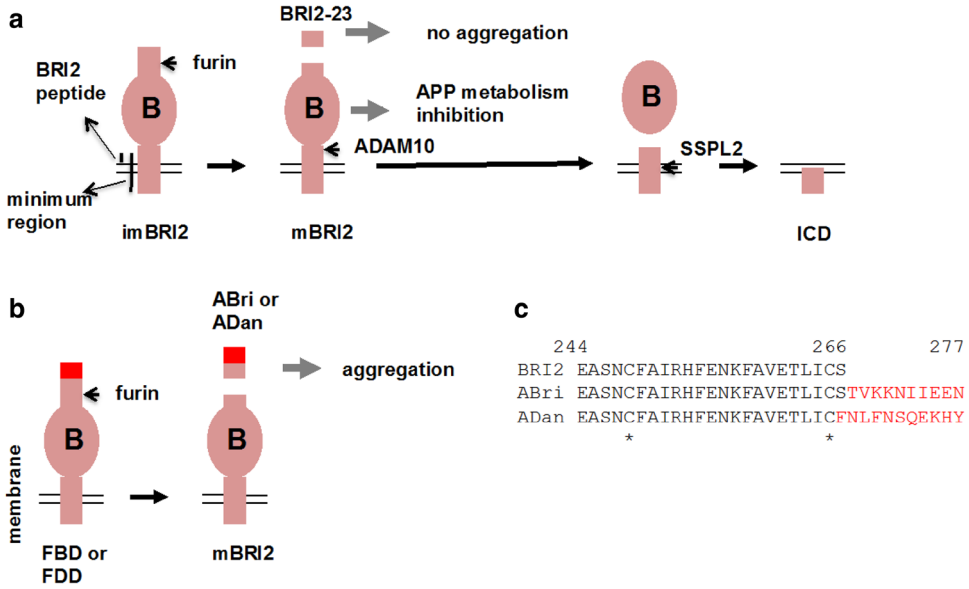

Fig. 3 Illustration of BR2 processing. **a** Successive proteolysis of BRI2. Immature BRI2 (imBRI2) is first processed by furin-like protease and releases the C-terminal BRI2-23 peptide, leaving mature BRI2 (mBRI2) on membrane. BRI2-23 does not aggregate. mBRI2 binds and inhibits APP processing. This mBRI2 is further processed by ADAM10, releasing the BRICHOS domain (indicated as B). Remaining short segment is further cleaved by SSPL2a/b to release the intracellular domain (ICD). Approximate positions of minimum region required for BRI2-APP interaction, and BRI2 peptide are marked as black lines. **b** FBD and FDD mutation fuse short peptides (red) to the C-terminus of BRI2. Cleavage by furin produces ABri or ADan peptides for FBD or FDD, respectively, both of which form amyloid deposits. **c** Amino acid sequences of BRI2-23, ABri, and ADan. The numbers on the top are amino acid number of human BRI2. Amino acids added de novo are written in red. Two cysteines marked by asterisks form an intramolecular disulfide bond

amyloid deposits. The peptide sequence of the amyloid in the brain of patients revealed an existence of a stop codon mutation of *BRI2* gene, which gives additional de novo 11 amino acids produced by the read through [29]. Since this stop codon mutation co-segregates with the disease in the affected pedigree, BRI2 mutation was concluded to be the cause of FBD.

Similarly, a closely related but distinct familial dementia (familial Danish dementia—FDD) has also a mutation in the same *BRI2* gene [42]. FDD mutation has 10-nucleotide duplication at the last codon before the stop codon of BRI2, which changes the last amino acid and again adding de novo 11 amino acids. The newly created amino acid sequences of FBD and FDD mutations are totally unrelated to each other. In both cases, amyloids were formed from the peptides made of BRI2-23 fused to de novo amino acids (Fig. 3b, c).

FBD and FDD are unique in that, in addition to amyloidosis, they share NTFs, which is one of the three key features of AD: first, since there is no sequence similarity among FBD and FDD peptides (ABri and ADan, respectively) and Aβ; second, since all three diseases cause peptide aggregations, NFTs, and dementia, the conventional wisdom was that the amyloid deposits, regardless of their sequences, are the common cause of AD, FBD, and FDD [43, 44]. This idea fits nicely to Amyloid Cascade Theory. However, it was also possible that the common symptoms were caused by APP: APP is involved in all three, because BRI2 regulates APP metabolism through binding.

FDD model mice show memory loss and defect of long-term potentiation (LTP)

The knock-in mice analogous to human FDD patients did not produce any detectable ADan amyloid deposition, accumulation of Aβ, or NTFs [45]. Since Danish mutation of BRI2 slows the processing of C-terminal peptide [46], BRI2 protein could have been missorted. Surprisingly, the result of mouse brain organelle fractionation showed no aberrant accumulation of the FDD mutant protein in particular organelle; rather, it simply disappeared from all fractions where BRI2 is normally found, including synaptic fractions. The FDD mice displayed loss of memory in radial maze and showed decrease of LTP in hippocampal slices, which reflects impaired learning and memory. Heterozygous BRI2 knockout mice showed similar memory defects. Taken together, the memory deficits found in FDD mice are more likely to be caused by haploinsufficiency of functional BRI2 than by amyloid deposits or NFTs (Fig. 4a) [47].

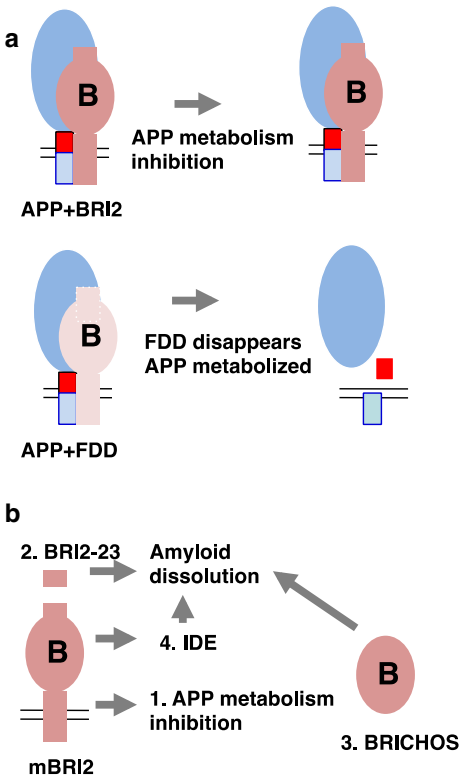

Fig. 4 Modes of action of BRI2 and mutant BRI2. **a** Probable mode of action of the FDD mutant of BRI2. Whereas wild-type BRI2 binds APP and stabilizes the complex (APP + mBRI2), the FDD mutant disappears, making APP unstable, ending up in its further proteolysis (APP + FDD). **b** While mature BRI2 inhibits APP metabolism (1), other mechanisms, the BRI2-23 peptide (2), the BRICHOS domain (3), or insulin degrading enzyme (IDE) induced by BRI2 (4) could dissolve amyloid deposits

Both alleles of APP are required for the memory deficits

When heterozygous APP knockout mice were crossed with FDD mice, the crossed mice did not show the memory defects found in FDD mice. Considering that FDD mice show memory deficits, and heterozygous APP knockout mice do not show any LTP loss in hippocampal slices, the memory defect found in FDD mice is mediated by APP [48].

Notably, there is three amino acid difference in the mouse Aβ amyloid region compared to the human counterpart, which makes murine Aβ unable to aggregate [49], which is why human APP, but not murine APP, is generally used to create AD model mice. The result that heterozygous APP knockout mice could recover the memory loss of FDD mice indicates that the memory defect in FDD has nothing to do with aggregated Aβ, because there is no human Aβ that can aggregate.

BRI2-derived peptide blocks β secretase and ameliorates memory deficits in FDD mice

The minimal region of BRI2-APP interaction was determined as N-terminal 102 amino acids or less by deletion mutants. Multiple peptides covering the juxtamembrane region were synthesized and tested for their effect on APP metabolism. Only peptides covering amino acids 85–94 inhibited β and α secretase of cultured mammalian cells when the peptides were added to the culture media. Alanine scanning of the peptide produced a slightly different peptide that inhibits β but not α secretase. This β secretase inhibiting peptide recovered the memory deficits observed in FDD mice, hinting a therapeutic application of BRI2 [32].

Conclusion

BRI2 is an anti-Alzheimer gene. Experiments by others using AD model mice also support the same conclusion. Virus-mediated gene transfer of BRI2 reduced Aβ burden of AD model mice [50], though they explain the effect which was caused by BRI2-23 peptide, because BRI2 without the BRI2-23 portion did not work. This might be due to inefficient sorting of the BRI2 mutant due to the missing BRI2-23 segment [34]. Transgenic FDD mice crossed with an AD model mouse again showed reduced Aβ [51], and the authors attributed the reduction to the interaction between ADan and Aβ. BRI2 transgenic crossed with an AD model mouse again showed reduced Aβ deposits, and they attributed the effect to insulin degrading enzyme (IDE) [52]. Despite differences, all of them showed that BRI2 works as an anti-Alzheimer gene in different animal context. In all these experiments, Aβ accumulation was used to assess their anti-Alzheimer effect, whereas, in addition to Aβ, other metabolites of APP and memory were used in ours [33, 47].

It is possible that different regions of BRI2 play additional roles in mice. In this regard, the BRICHOS domain of BRI2, which is not required for the interaction of BRI2 and APP, is reported to halt the aggregate formation of BRI2-23 and Aβ40 [53, 54]. The report that BRICHOS domain is immunologically detected in Aβ aggregates in human AD patient [55] further underscores close relationship between BRI2 and AD (Fig. 4b).

Finally, it should be stressed that Aβ deposits itself may not be the appropriate measure of AD progression. As described above, Aβ deposits in human patient brain do not correlate well with disease stages. Transgenic animals harboring BRI2 fused with Aβ showed massive accumulation of Aβ with no cognitive deficits [56]. Neuron-specific conditional knockout mice of PSEN1 and PSEN2, whose Aβ is significantly reduced, still show neuronal degeneration and impaired memory [57, 58]. All these do not sit well

with the amyloid cascade theory. There is more to AD other than amyloid deposition, and we believe that BRI2 plays a crucial part in it.

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